FRONTIERS IN NEUROLOGY

OPINION ARTICLE
published: 09 March 2012
doi: 10.3389/fneur.2012.00034

Revisiting baclofen for the treatment of severe chronic tinnitus

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Subjective tinnitus is a phantom sensation of sound, which has been estimated to occur in 25.3% of people in the USA, with 7.9% experiencing it frequently (Shargorodsky et al., 2010). Drugs are one of a number of potential treatment avenues for severe chronic tinnitus. However, to date, there is relatively little agreement about which particular drugs might be best used to alleviate the condition (see Darlington and Smith, 2007; Hoekstra et al., 2011 for reviews).

On the assumption that chronic tinnitus is associated with neuronal hyperactivity at different levels of the central auditory pathways, such as the dorsal cochlear nucleus, the inferior colliculus, and the auditory cortex (see Moller, 2000; Eggermont and Roberts, 2004; Eggermont, 2005; Kaltenbach, 2006; Roberts et al., 2010 for reviews; see Dong et al., 2010; Middleton et al., 2011; Vogler et al., 2011; Wang et al., 2011 and Mulders and Robertson, 2011 for recent examples), drugs that increase inhibitory neurotransmission or block excitatory neurotransmission, are often used. Aside from anti-epileptic drugs, which are an obvious choice, the anti-spasticity agent and $GABA_B$ receptor agonist, baclofen, has also been used occasionally.

Unfortunately, as Hoekstra et al. (2011) concluded in a recent review, the evidence supporting the efficacy of anti-epileptic drugs in treating tinnitus is not very convincing. Even less convincing is the evidence supporting the use of baclofen. The only published clinical trial of baclofen in patients with tinnitus, yielded inconsistent results. The patients' subjective ratings of tinnitus were significantly reduced following drug administration compared to before drug administration; however, there was no significant difference compared to the placebo group (Westerberg et al., 1996). Nonetheless, interest in the possible use of baclofen to treat tinnitus remained (Møller, 1997). One potential problem with the trial was that the patients in the baclofen arm of the study appeared to have more severe tinnitus to begin with. Another was that the study was potentially underpowered statistically due to the inclusion of several different types of tinnitus, some of which might not have responded to the drug (Møller, 1997). The possibility that the study was underpowered was carefully acknowledged by the authors themselves, who performed power calculations for different scenarios (Westerberg et al., 1996). In addition, Westerberg et al. (1996) apparently used racemic baclofen (i.e., a mixture of the L- and D-isomers of baclofen, also known as *R*- and *S*-isomers), which was the only licensed form in 1996 (Szczepaniak and Møller, 1995), and D-baclofen has been reported to be less potent than L-baclofen in reducing tone- and click-evoked hyperexcitability in neurons of the inferior colliculus (Szczepaniak and Møller, 1995, 1996).

In fact, a number of studies have reported that D-baclofen can reduce the effects of L-baclofen. This has been reported in the trigeminal nucleus (Terrence et al., 1983; Fromm et al., 1990), but not in the hippocampus or neocortex (Howe and Zieglgänsberger, 1986). In the spinal cord, D-baclofen has been reported to antagonize the effects of L-baclofen (Sawynok and Dickson, 1984, 1985). In a double blind crossover trial with 15 patients suffering from trigeminal neuralgia, in 9 patients L-baclofen was reported to be five times more effective in relieving the symptoms than racemic baclofen (Fromm and Terrence, 1987). In addition, the adverse side effects of L-baclofen were better tolerated than those of the racemic baclofen (Fromm and Terrence, 1987). Although the idea that D-baclofen is an antagonist, at least at some $GABA_B$ receptors, is still unresolved (Froestl, 2010), at the very least it can be concluded that its agonist effects are much less potent than L-baclofen, which appears to be the case in the inferior colliculus (Szczepaniak and Møller, 1995, 1995). This raises the possibility that the use of racemic baclofen to treat tinnitus, as was the case in the study by Westerberg et al. (1996), may have actually undermined the effects of the L-baclofen. An obvious question is why racemic baclofen would be manufactured if there was evidence that D-baclofen is less potent than L-baclofen? One consideration is probably that racemic baclofen is easier to manufacture, because the separation of the L- and D-isomers requires additional steps.

The potential utility of L-baclofen, as opposed to D-baclofen or racemic baclofen, is supported by a recent study in which we found that L-baclofen dose-dependently reduced the behavioral signs of chronic tinnitus in an animal model caused by acoustic trauma (Zheng et al., 2012). Although the lowest effective dose for clear suppression of tinnitus was 3 mg/kg, using the dose adjustment calculation employed by the FDA to calculate human equivalent doses (Regan-Shaw et al., 2007), this was approximately equivalent to 34.1 mg/day for a 70-kg adult. This is above the effective dose of 6–12 mg of L-baclofen reported by Fromm and Terrence (1987) for the treatment of trigeminal neuralgia but is lower than the twice daily 20 or 30 mg doses of racemic baclofen employed by Westerberg et al. (1996) in patients with tinnitus, which were the highest doses used in the second and third weeks of their study (in the first week they used 10 mg twice daily). Therefore, the effective dose of L-baclofen in our animal model study was within the dose range of racemic baclofen that has been used in humans.

While baclofen is not likely to be a drug of first choice for tinnitus due to its adverse side effects, such as sedation, confusion, and dizziness (Jorns and Zakrzewska, 2007), the significance of the potential underestimation of $GABA_B$ receptor agonists for the treatment of tinnitus, extends beyond baclofen itself. Arbaclofen placarbil is a novel L- (or R-)

baclofen prodrug with improved pharmacokinetics that may be useful in the treatment of neurological disorders (Lal et al., 2009). There is also a new generation of novel $GABA_B$ receptor agonists, such as CGP7930 (Adams and Lawrence, 2007), which do not have the adverse side effects of baclofen but which may be useful for the treatment of tinnitus. It would unfortunate if the extensive use of racemic baclofen prevented these new $GABA_B$ receptor agonists from being investigated for their efficacy against tinnitus.

ACKNOWLEDGMENTS

This research was supported by grants from the Jean Cathie Estate and the New Zealand Neurological Foundation grant to Paul F. Smith, Yiwen Zheng, and Cynthia L. Darlington.

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Received: 08 February 2012; accepted: 21 February 2012; published online: 09 March 2012.
*Citation: Smith PF, Zheng Y and Darlington CL (2012) Revisiting baclofen for the treatment of severe chronic tinnitus. Front. Neur. **3**:34. doi: 10.3389/fneur.2012.00034*
This article was submitted to Frontiers in Neuro-otology, a specialty of Frontiers in Neurology.